BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 31/485

A2

(11) International Publication Number: WO 87/ 01282

(43) International Publication Date: 12 March 1987 (12.03.87)

(21) International Application Number: PCT/US86/01847

(22) International Filing Date: 8 September 1986 (08.09.86)

(31) Priority Application Number: 773,213

(32) Priority Date: 6 September 1985 (06.09.85)

(33) Priority Country: US

(71) Applicant: KEY PHARMACEUTICALS, INC. [US/US]; 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(72) Inventors: TUTTLE, Ronald, R. ; HOWES, John ; Key Pharmaceuticals, Inc., 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(74) Agents: WEGNER, Harold, C. et al.; Wegner & Bretschneider, P.O. Box 18218, Washington, DC 20036 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE, DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: METHOD AND COMPOSITION FOR PROVIDING SUSTAINED OPIOID ANTAGONISM

(57) Abstract

Prolonged opioid antagonism is provided by injection of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine. Such injection is useful for a variety of remedial and prophylactic uses. An injectable dosage form of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine can be provided in a kit form with instructions as to use.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GA	Gabon	MR	Mauritania
AU	Australia	GB	United Kingdom	MW	Malawi
BB	Barbados	HU	Hungary	NL	Netherlands
BE	Belgium	IT	Italy	NO	Norway
BG	Bulgaria	JP	Japan	RO	Romania
BR	Brazil	KP	Démocratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
DE	Germany, Federal Republic of	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America
FI	Finland	MG	Madagascar		
FR	France	ML	Mali		

METHOD AND COMPOSITION FOR PROVIDING SUSTAINED OPIOID ANTAGONISM

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to a method and composition for providing sustained opioid narcotic antagonism. In particular, the invention is directed to use of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine to provide opioid antagonism while preventing renarcotization of the subject.

2. Description of the Prior Art

Opioid antagonists presently are used to counter the effects of opioid narcotics. The compound naloxone, a pure opioid antagonist, is used in treating opioid drug overdoses, for example. However, use of naloxone suffers from a disadvantage in that the active duration of naloxone is only about 45-90 minutes. Thus, renarcotization of the subject following administration of the naloxone can occur. This happens when the opioid is not metabolized as quickly as the naloxone. Thus, a subject apparently fully revived by treatment with injectable naloxone can later suffer from reappearing opioid effects, i.e., renarcotization, a condition which at best results in the nuisance of continued medical supervision and repeated injections of naloxone, and at worst is life-threatening if not recognized and treated.

The compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is a known pure opioid antagonist. The compound is described in Fishman U.S. Patents 3,814,768 and 3,896,226. The disclosures of these patents are incorporated herein by reference. Fishman '226 discloses a preferred oral dosage of

0.1-10.0 mg of 6-methylene-6-desoxy dihydro-morphine and -codeine derivatives per kg body weight, and mentions a narcotic antagonist effect persisting for 8-12 hours. A parenteral dose of 0.02-2 mg per kg body weight also is disclosed.

Hsiao and Dixon, Research Communications in Chemical Pathology and Pharmacology, Vol. 42, No. 3, pp.449-54, Dec. 1983, describes a process for detecting 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in human plasma. The results show that a pharmacologically active concentration of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine can remain in the plasma of a patient for three days.

SUMMARY OF THE INVENTION

The present invention provides a method and composition yielding sustained opioid antagonism properties without renarcotization.

The invention further provides a method and composition for opioid narcotic antagonism which can be used both remedially and prophylactically in a variety of procedures.

In accordance with a first aspect of the invention, there is provided a method of treating a subject who has undergone opioid-induced general anesthesia, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid anesthetic, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

A second aspect of the invention provides a method of treating a subject who is suffering from narcotic effects of an opioid drug overdose, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-

cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to relieve the narcotic effects of the opioid drugs, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

A further aspect of the invention provides a method of treating a patient who has undergone opioid analgesia for a surgical or diagnostic procedure, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid analgesic, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine providing a sufficiently sustained antagonism so that renarcotization of the subject is prevented.

Yet another aspect of the invention is directed to a method of treating a subject undergoing a surgical or diagnostic procedure, comprising administering to the subject an opioid analgesic in an amount sufficient to relieve discomfort from the surgical or diagnostic procedure; performing the surgical or diagnostic procedure; and injecting the subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine after completion of the procedure, the 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine being injected in an amount sufficient to antagonize the narcotic effects of the opioid analgesic and to provide sustained narcotic antagonism so that renarcotization of the subject is prevented and the subject may be released from a physician's attendance upon the injection of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine taking effect.

A still further aspect of the invention provides a method of preventing respiratory depression in a subject undergoing epidural opioid regional analgesia,

comprising injecting said subject with an amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine sufficient to antagonize respiratory depressive effects of the epidural opioid analgesic.

Another aspect of the invention is directed to a method of antagonizing opioid narcotic effects in a baby whose mother is given an opioid analgesic during delivery, comprising administering the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine to the baby by injection through the umbilical vein, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine being sufficient to antagonize the narcotic effects and provide sustained narcotic antagonism so that renarcotization is prevented.

According to a still further aspect of the invention, there is provided a method of treating a subject suffering from narcotic effects of endogenous opioids, comprising injecting the subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the endogenous opioid, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

Another embodiment of the invention is directed to a kit which comprises:

(a) An opioid analgesic suitable for providing relief of discomfort in a subject undergoing a surgical or diagnostic procedure.

(b) an intravenous dosage form containing a dosage unit capable upon administration to the subject of providing a continuous prolonged presence in the blood stream of a pure opioid antagonist for a period of at least about eight hours which comprises in a

pharmaceutically inert diluent 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid analgesic in the subject over said prolonged period, whereby a sufficiently sustained narcotic antagonism effect is provided over said prolonged period, whereby during said prolonged period renarcotization of the subject is avoided; and

(c) instructions on the administration of the active ingredient for said prolonged presence.

A still further embodiment of the invention provides a method of antagonizing opioid narcotic effects in a subject having need of opioid narcotic antagonism, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the opioid narcotic effects in the subject, the amount of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine being sufficient to provide a sustained narcotic antagonism such that renarcotization of the subject is prevented for a prolonged period of at least about eight hours.

A useful dosage range is in the amount of about 0.1-25 mg of the active ingredient.

BRIEF DESCRIPTION OF THE DRAWING

The drawing is a graph showing results obtained in the tests described below.

DETAILED DESCRIPTION OF THE INVENTION

The compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is a specific antidote for opioid narcosis. Like the compound naloxone, 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is a pure opioid antagonist,

exerting no opioid effects. Like naloxone, it is effective against both endogenous opioids, e.g. endorphins, and natural or synthetic exogenous opioids, e.g. morphine and Demerol.

Injection of a subject with 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxydihydronormorphine provides fast acting and sustained opioid antagonism. These properties will make 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxydihydronomorphine desirable for uses where naloxone presently cannot be used, as well as improve treatment in fields where naloxone presently is used such as the treatment of drug overdose cases. The long duration of the opioid antagonism also decreases the need for physician attendance and medical supervision.

The amount of 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxydihydronormorphine administered to a subject will be from about 0.1-25 mg. It is preferred to give the 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in doses of about 1 mg with repeated injections if necessary. The injectable compositions are made by dissolving the active ingredient in a suitable carrier, such as water or saline. Further components such as preservatives and acid for pH adjustment can be added if desired. The order of addition to the carrier is not important.

One specific injectable composition contemplated includes the following per each ml of injectable composition: 1.108 mg 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine hydrochloride; 1.8 and 0.2 mg respectively of the preservatives methylparaben and propylparaben; 9 mg USP grade NaCl; HCl to provide a pH of 3.9; and sterile water. It should be understood that the term 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is used in this application to refer to the compound itself as well as pharmaceutically effective derivatives such as the

acid addition salt noted in the listing above.

It is desirable for the composition to be stored in containers ready for use, such as ampules or prefilled syringes containing about 1 ml of the composition outlined above. Such containers can be made part of a kit which would include the container as well as instructions for treatment. The kit also could hold containers of an opioid analgesic to be used in minor surgical or diagnostic proceedings (described below) if desired.

There are a number of remedial uses for injectable 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine, i.e. for reversing the effects of previously administered opioids. Injectable 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine could be used for treatment of victims of opioid drug overdose. Currently, naloxone is injected to revive such overdose victims. However, the short duration of naloxone's opioid antagonistic effect can result in renarcotization of the patient, sometimes leading to loss of life. The present compound's increased duration of antagonistic activity (at least 6, preferably 8-9 hours) helps prevent renarcotization until the opioid has been metabolized. The injectable composition could be distributed in the form of prefilled syringes with suitable instructions. The safety of the present compound would allow the inclusion of a sufficient amount of active ingredient so that self-administration could be possible.

Injectable 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine expands the use of opioids for general anesthesia. At present, opioid general anesthesia is reserved for high-risk major surgery such as open heart surgery. One main reason why opioid general anesthesia is not used for other types of major surgery is the problem of dealing with potential

post-operative respiratory depression from the opioid. Injection of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine to revive the patient helps to alleviate this problem by providing opioid antagonism (i.e., against respiratory depression) for a period of time sufficient for the opioid anesthetic to be metabolized.

Injectable 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxydihydronormorphine is also useful in diagnostic and minor surgical procedures which are painful or anxiety producing, and thus require some analgesic during the procedure, but require no analgesia when the procedure is finished. Such procedures include, for example, lancing boils, setting dislocated shoulders, various kinds of dental work, certain radiological procedures, endoscopies of the gastrointestinal tract, endoscopies of the urinary system and bronchoscopies. Injectable 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine will allow the use of opioid analgesics for such procedures, followed by injection of the 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine to bring the patient out of the analgesia. 6-methylene-6-desoxy-N-cycloporpylmethyl-14-hydroxydihydronomorphine reduces the possibility of renarcotization so that the patient can go home without having to wait for the analgesic to wear off. This makes such surgical procedures much more convenient and less costly for patients. Further, the procedures can be conducted with sufficient analgesia to provide optimum patient comfort.

Injection of 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxydihydronormorphine also can be used for treating newly delivered babies. Many hospitals administer Demerol to delivering mothers. The Demerol is transmitted to the baby, making it dopey. Injection of 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxy-dihydronormorphine through the umbilical vein upon

delivery helps counter the opioid narcotic effects of the Demerol in the infant.

Injectable 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine also is useful in remedying the effects of endogenous opioids. Thus, it is useful in treating shock and neural trauma.

Injectable 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine also finds use in prophylactic applications, for example during surgery involving epidural opioid regional analgesia. Epidural opioid regional analgesia involves application of an opioid directly to the spinal cord in a high concentration. This procedure produces complete relief of pain supplied by pain conducting nerves below the site of epidural application. The result is like that of a spinal done with local anesthetics, except the disadvantage of paralysis is not present. A major problem with the epidural opioid technique is unpredictable respiratory depression which can occur if the opioid migrates from the spinal cord to the brain. Injection of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine would provide protection against this problem through the long-lasting opioid antagonistic properties, which are sufficient to counteract any opioid migrating to the brain. However, the 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine injected would not significantly affect the high concentration of the opioid provided at the spinal cord.

The unexpected long duration of action of nalmefene makes it of value in the treatment of pets, zoo animals and commercially important animals such as cattle and sheep.

Because of nalmefene's long duration of action it is possible to give animals very large doses of opioids that will allow painful procedures to be done on these animals. After completion of the procedure the opioid

induced narcosis can be rapidly and completely reversed. In contrast to other opioid antagonists available i.e. naloxone, with nalmefene there is no fear of renarcotization.

Particular applications are:

Pets

The veterinary treatment of injured dogs. For example, a dog hit by a car that is in great pain can have pain relieved by large doses of an opioid and any surgical repairs can be done while the dog is under the influence of the opioid. Then the opioid can be reversed by nalmefene and the owner can take home a fully revived pet.

Zoo Animals

These large animals such as deer, springbuck, onyx and rhinoceros are immobilized by the zoo's veterinary staff with opioids delivered from dartguns. This immobilization permits the vet to carry out minor surgical procedures. Nalmefene, as in the dog, will rapidly and completely reverse the opioid without fear of renarcotization. Nalmefene is lifesaving in these animals because if they renarcotize they can become hyperthermic and die.

Cattle and Sheep

Branding of these animals is painful and inhumane. Branding could be carried out humanely by doing it while the animal is heavily narcotized with an opioid. As in the above two cases, the narcotic can be reversed with nalmefene in cows or sheep rapidly and completely without fear of renarcotization. Thus the animals can be immediately returned to the herd.

Example

The study was designed to test the duration of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine action by pretreating subjects with the

antagonist and then challenging with periodic doses of a short-acting opioid agonist (fentanyl).

Methods. Six healthy males (ages 23-28) were pretreated in random double-blind fashion on each of four separate days with a saline placebo, 0.5 mg, 1.0 mg, or 2.0 mg 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine intravenously. Subjects were tested before and after this pre-treatment, and following opioid challenge with each of five doses of fentanyl (2 µg/kg) at 1, 2, 4, 6, and 8 hours afterwards. Respiratory depression was identified by the CO_2 rebreathing method of Read. Ventilatory and occlusion pressure responses were analyzed by relating slopes of the increased minute ventilation (VE) and occlusion pressure ($P_{0.1}$) to end -tidal CO_2, and by recording VE and $P_{0.1}$ at a fixed level of increased CO_2 (60 mmHg) during rebreathing. Analgesia to experimental pain was assessed by recording the time to onset of unbearable pain (tolerance) during submaximal tourniquet-induced ischemia.

Results. At one hour following placebo pretreatment, fentanyl produced nasal itching, mild nausea, drowsiness, and marked respiratory depression compared to the control state (Table 1) below. Both VE60 (29% of control) and $P_{0.1}60$ (41% of control) were significantly decreased ($P<_{0.01}$) as were the sloped of the ventilatory and occlusion pressure responses (VE/PCO_2, $P_{0.1}/PCO_2$) which were 51 and 55% of control, respectively. Each subsequent fentanyl dose produced a similar degree of respiratory depression as illustrated by VE60 (Fig.1). Pretreatment with 2.0 mg 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine completely prevented the subjective and respiratory effects of fentanyl for the entire 8 hours of the experiment. 6-methylene-6-desoxy-N-cycloporpylmethyl-14-hydroxydihydronormorphine (1.0 mg) significantly blunted the respiratory depression over the same

period when compared to placebo pretreatment, but VE60 values at 6 and 8 hours were depressed significantly (P< 05) to 66 and 61% of control. The antagonist effects of the lowest 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine dose (0.5 mg) persisted for about 4 hours, at which time VE60 was 64% of control.

In the absence of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine, each fentanyl dose produced consistent increases in tolerance to pain (44-55% above control). 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine pretreatment abolished this analgesic response in a dose-related time course which mirrored the respiratory effects almost exactly.

Table 1. Ventilatory Responses

	Control	Fentanyl
VE60 ($l.min^{-1}$)	45.9	13.4*
	(6.3)	(2.3)
$P_{0.1}60$ (cm H_2O)	8.0	3.3*
	(1.2)	(0.4)
VE/PCO_2 ($l.min^{-1}.mmHg^{-1}$)	3.36	1.73*
	(0.47)	(0.26).
$P_{0.1}/PCO_2$ (cm $H_2O.mmHg^{-1}$)	0.58	0.32*
	(0.09)	(0.07)

Values are Mean ± SEM for six subjects

*p<0.01 denotes significant difference from control.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a subject who has undergone opioid-induced general anesthesia, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid anesthetic, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxy-dihydronormorphine providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

2. The method of claim 1, wherein the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydi-hydronormorphine is from about 0.1 to about 25 mg.

3. A method of treating a subject who is suffering from narcotic effects of an opioid drug overdose, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydi-hydronormorphine in an amount sufficient to relieve the narcotic effects of the opioid drugs, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydi-hydronormorphine providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

4. The method of claim 3, wherein the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydi-hydronormorphine is from about 0.1 to about 25 mg.

5. A method of treating a patient who has undergone opioid analgesia for a surgical or diagnostic procedure, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid analgesic, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine providing a sufficiently

sustained antagonism so that renarcotization of the subject is prevented.

6. The method of claim 5, wherein the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is from about 0.1 to about 25 mg.

7. A method of treating a subject undergoing a surgical or diagnostic procedure, comprising administering to the subject an opioid analgesic in an amount sufficient to relieve discomfort from the surgical or diagnostic procedure; performing the surgical or diagnostic procedure; and injecting the subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxy-dihydronormorphine after completion of the procedure, the 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine being injected in an amount sufficient to antagonize the narcotic effects of the opioid analgesic and to provide sustained narcotic antagonism so that renarcotization of the subject is prevented and the subject may be released from a physician's attendance upon the injection of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine taking effect.

8. A method of preventing respiratory depression in a subject undergoing epidural opioid regional analgesia, comprising injecting said subject with an amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine sufficient to antagonize respiratory depressive effects of the epidural opioid analgesic.

9. The method of claim 8, wherein the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is from about 0.1 to about 25 mg.

10. A method of antagonizing opioid narcotic effects in a baby whose mother is given an opioid analgesic during delivery, comprising administering the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine to the baby by injection

through the umbilical vein, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine being sufficient to antagonize the narcotic effects and provide sustained narcotic antagonism so that renarcotization is prevented.

11. The method of claim 10, wherein the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is from about 0.1 to about 25 mg.

12. A method of treating a subject suffering from narcotic effects of endogenous opioids, comprising injecting the subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the endogenous opioid, the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

13. The method of claim 12, wherein the amount of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine is from about 0.1 to about 25 mg.

14. A kit which comprises:

(a) An opioid analgesic suitable for providing relief of discomfort in a subject undergoing a surgical or diagnostic procedure.

(b) an intravenous dosage form containing a dosage unit capable upon administration to the subject of providing a continuous prolonged presence in the blood stream of a pure opioid antagonist for a period of at least about eight hours which comprises in a pharmaceutically inert diluent 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid analgesic in the subject over said prolonged period, whereby a sufficiently

sustained narcotic antagonism effect is provided over said prolonged period, whereby during said prolonged period renarcotization of the subject is avoided; and

(c) instructions on the administration of the active ingredient for said prolonged presence.

15. A method of antagonizing opioid narcotic effects in a subject having need of opioid narcotic antagonism, comprising injecting said subject with the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the opioid narcotic effects in the subject, the amount of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine being sufficient to provide a sustained narcotic antagonism such that renarcotization of the subject is prevented for a prolonged period of at least about eight hours.

16. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition useful for treating a subject who has undergone opioid-induced general anesthesia by antagonizing the narcotic effects of the opioid anesthetic and providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

17. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition useful for treating a subject who is suffering from narcotic effects of an opioid drug overdose by antagonizing the narcotic effects of the opioid drugs and providing a sufficiently sustained narcotic antagonism so that renarcotization of the subject is prevented.

18. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition useful for

treating a subject who has undergone opioid analgesia for a surgical or diagnostic procedure by antagonizing the narcotic effects of the opioid analgesic and providing a sufficiently sustained antagonism so that renarcotization of the subject is prevented.

19. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition useful for treating a subject who is undergoing epidural opioid regional analgesia by antagonizing respiratory depressive effects of the epidural opioid analgesic.

20. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition for treating a baby whose mother is given an opioid analgesic during delivery, by injection through the umbilical vein to antagonize the narcotic effects of the opioid analgesic in the baby and provide sustained antagonism so that renarcotization is prevented.

21. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition useful for treating a subject who is suffering from the effects of endogenous opioids by antagonizing the narcotic effects of the endogenous opioid and providing a sufficiently sustained antagonism so that renarcotization of the subject is prevented.

22. Use of 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine for preparing an injectable pharmaceutical composition useful for treating a subject who is in need of opioid narcotic antagonism, the narcotic antagonism being sufficient to prevent renarcotization of the subject for at least eight hours.

23. A kit which comprises:

(a) an intravenous dosage form containing a dosage unit capable upon administration to

the subject of providing a continuous prolonged presence in the blood stream of a pure opioid antagonist for a period of at least about eight hours which comprises in a pharmaceutically inert diluent 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid analgesic in the subject over said prolonged period, whereby a sufficiently sustained narcotic antagonism effect is provided over said prolonged period, whereby during said prolonged period renarcotization of the subject is avoided; and

(b) instructions on the administration of the active ingredient for said prolonged presence.

24. A kit which comprises:

(a) An opioid analgesic suitable for providing relief of discomfort in a subject undergoing a surgical or diagnostic procedure; and

(b) an intravenous dosage form containing a dosage unit capable upon administration to the subject of providing a continuous prolonged presence in the blood stream of a pure opioid antagonist for a period of at least about eight hours which comprises in a pharmaceutically inert diluent 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine in an amount sufficient to antagonize the narcotic effects of the opioid analgesic in the subject over said prolonged period, whereby a sufficiently sustained narcotic antagonism effect is provided over said prolonged period, whereby during said prolonged period renarcotization of the subject is avoided.

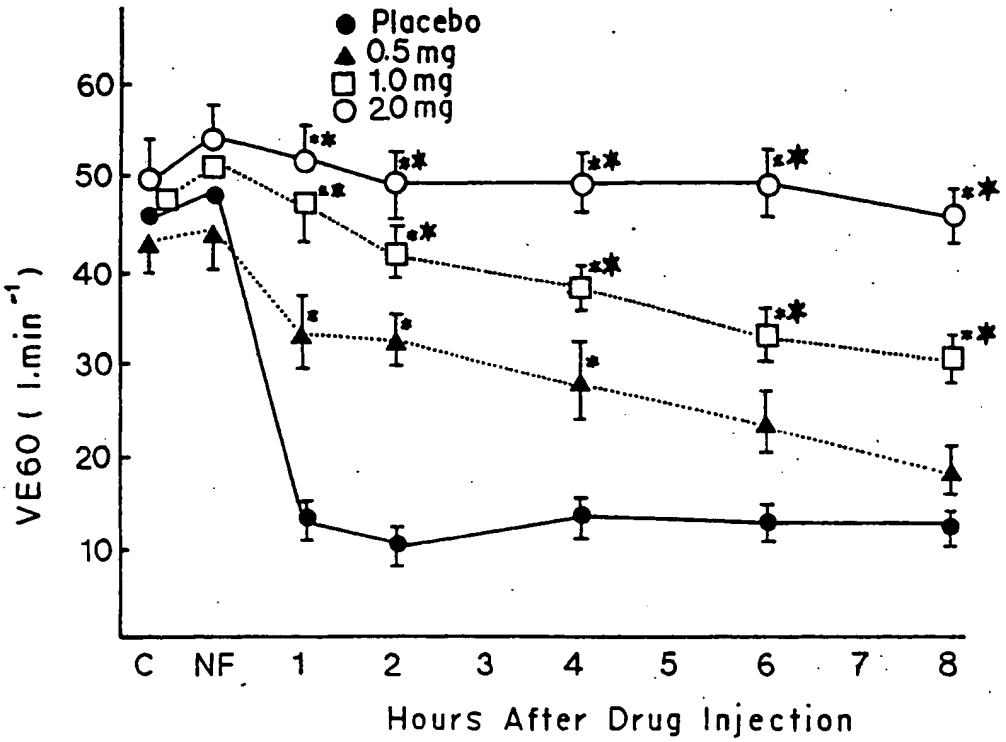

Fig. 1: Control (C) values for VE60 (Mean ±SEM) after placebo or 6-methylene-6-desoxy-N-cyclopropyl-methyl-14-hydroxydihydronormorphine (NF) pretreatment, and fentanyl challenge (2μg/kg) 1, 2, 3, 6, and 8 hours later.
*p<0.05; ✱p<0.01 denotes significant difference from placebo pretreatment.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 31/485

A3

(11) International Publication Number: WO 87/ 01282

(43) International Publication Date: 12 March 1987 (12.03.87)

(21) International Application Number: PCT/US86/01847

(22) International Filing Date: 8 September 1986 (08.09.86)

(31) Priority Application Number: 773,213

(32) Priority Date: 6 September 1985 (06.09.85)

(33) Priority Country: US

(71) Applicant: KEY PHARMACEUTICALS, INC. [US/US]; 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(72) Inventors: TUTTLE, Ronald, R. ; HOWES, John ; Key Pharmaceuticals, Inc., 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(74) Agents: WEGNER, Harold, C. et al.; Wegner & Bretschneider, P.O. Box 18218, Washington, DC 20036 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE, DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:

13 August 1987 (13.08.87)

(54) Title: METHOD AND COMPOSITION FOR PROVIDING SUSTAINED OPIOID ANTAGONISM

(57) Abstract

Prolonged opioid antagonism is provided by injection of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine. Such injection is useful for a variety of remedial and prophylactic uses. An injectable dosage form of the compound 6-methylene-6-desoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine can be provided in a kit form with instructions as to use.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
DE	Germany, Federal Republic of	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America
FI	Finland	MG	Madagascar		

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 86/01847

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/485

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Journal of Pharmaceutical Sciences, volume 73, no. 11, November 1984, (US), R. Dixon et al.: "Nalmefene: radio-immunoassay for a new opioid antagonist", pages 1645-1646, see page 1646, figure 1 and right-hand column, lines 39-43 --	14,16-24
X	Research Coomunications in Chemical Pathology and Pharmacology", volume 13, no. 4, April 1976, (New York, US), R.D. Heilman et al.: "An evaluation of the hot plate technique to study narcotic antagonists", pages 635-647, see the whole document --	14,16-24
X	Chemical Abstracts, volume 103, no. 23, 9 December 1985, (Columbus, Ohio, US), M.E. Michel et al.: "Binding of a new opiate antagonist, nalmefene, to rat brain membranes", see page 61, abstract 189569b, Methods Find. Exp. Clin. Pharmacol. 1985, 7(4), 175-7 ./.	14,16-24

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th May 1987	22 JUL 1987
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: M. VAN MOL

International Application No. PCT/US 86/01847

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	EP, A, 0140367 (KEY PHARMACEUTICALS) 8 May 1985, see page 1 --	14,16-24
X	Journal of Medicinal Chemistry, volume 18, no. 3, 1975 (US) E.F. Hahn et al.: "Narcotic antagonists. 4. Carbon-6 derivatives of N-substituted noroxymorphones as narcotic antagonists", pages 259-262, see page 259, left-hand column; page 260, right-hand column, lines 10-12; page 262, note (18) --	14,16-24
L	US, A, 4567185 (M.A. SACKNER) 28 January	

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers XX because they relate to subject matter not required to be searched by this Authority, namely:

XX Claims 1-13,15

See PCT Rule 39.1(iv):

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ..... because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

International Application No. PCT/US 86/01847

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	1986, see the whole document	21
	--	
X	WO, A, 83/03197 (THE ROCKEFELLER UNIVERSITY) 29 September 1983, see page 2, lines 20-24; page 3, lines 14-18; page 4, lines 1-9; page 10	21
	--	
X	Substance and Alcohol Actions/Misuse, volume 5, no. 2, 1984, Pergamon Press Ltd. (US), M.J. Katovich et al.: "A rapid, quantitative in vivo assay for narcotic antagonists", pages 87-95, see page 87	19
	--	
X	Research Communications in Chemical Pathology and Pharmacology, volume 42, no. 3, December 1983, (US) J. Hsiao et al.: "Nalmefene: Quantitation of a new narcotic antagonist in human plasma using high performance-liquid chromatography with electrochemical detection", pages 449-454, see pages 449-450 cited in the application	14,16-24
	--	
X	Chemical Abstracts, volume 88, no. 1, 2 January 1978, (Columbus, Ohio, US), E.S. Vizi et al.: "Agonist-antagonist interaction studies with morphine, 6-azidomorphine and oxymorphone dérivatives", see page 167, abstract 167b, Congr. Hung. Pharmacol. Soc. (Proc.) 1974 (Pub. 1976), 2(1, Symp. Analg.), 85-96	14,16-24
	--	
X	FR, A, 2160957 (J. FISHMAN) 6 July 1973, see the whole document & US, A, 3814768 (cited in the application)	14,16-24
	--	
X	Fed. Proceed. volume 43, no. 4, 1984, C.B. Mash et al.: "Studies on nalmefene, an opioid antagonist", page 967, abstract 3987, see abstract	14,16-24
	--	
X	Goodman and Gilman's The Pharmacological basis of therapeutics", 7th Edition 1985, Macmillan Publishing Company, (New York, US), pages 524-527 and 573-574, see pages 524-527 and 573-574	14,
	-- ./.	

International Application No. PCT/US 86/01847

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	GB, A, 769517 (MERCK & CO) 6 March 1957, see the whole document	14,24
A	US, A, 3493657 (M.J. LEWENSTEIN) 3 February 1970, see the whole document	14,19,24
A	EP, A, 0144243 (RECKITT AND COLMAN PRODUCTS) 12 June 1985, see page 5, lines 4-10	14,16-24
X,P	Anesthesiology, volume 64, no. 2, February 1986, T.J. Gal M.D. et al.: "Prolonged antagonism of opioid action with intravenous nalmefene in man", pages 175-180, see the whole document	14,16-24
X,P	Clin. Pharmacol. Ther., volume 39, no. 1, January 1986, R. Dixon et al.: "Nalmefene: Intravenous safety and kinetics of a new opioid antagonist", pages 49-53, see the whole document	14,16-24
T	Journal Clin. Pharmacol., volume 26, no. 7, September/October 1986, L.R.C. Moore et al.: "Antagonism of fentanyl-induced respiratory depression with nalmefene", page 558, see abstract	14,16-24
T	Clin. Pharmacol. ther., volume 40, no. 5, November 1986, T.J. Gal, M.D. et al.: "Prolonged blockade of opioid effect with oral nalmefene", pages 537-542, see the whole document	14,16-24

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 86/01847 (SA 14782)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/07/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 8303197	29/09/83	EP-A-	0103636	28/03/84
		CA-A-	1212323	07/10/86
FR-A- 2160957	06/07/73	DE-A,C	2257715	30/05/73
		US-A-	3814768	04/06/74
		US-A-	3896226	22/07/75
		GB-A-	1411129	22/10/75
		CA-A-	974235	09/09/75
		CH-A-	578568	13/08/76
		JP-A-	48058000	14/08/73
GB-A- 769517		None		
US-A- 3493657	03/02/70	None		
EP-A- 0144243	12/06/85	AU-A-	3632984	13/06/85
		GB-A-	2150832	10/07/85
		JP-A-	60146824	02/08/85
		US-A-	4582835	15/04/86